PATENT SPECIFICATION

763,044

Inventor: WILLIAM ROBERT BOON

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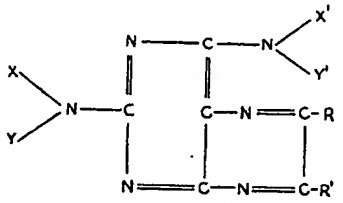
COMPLETE SPECIFICATION

Pteridin Derivatives

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pteridin derivatives and to processes for the manufacture of the said new pteridin derivatives.

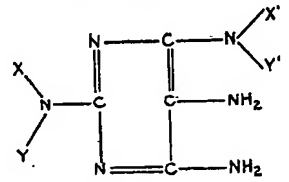
The new pteridin derivatives of our invention are compounds of the formula:



wherein X and X^1 stand for alkyl and Y and Y^1 stand for alkyl or hydrogen, wherein X and Y and X^1 and Y^1 may optionally be joined to form together with the adjacent nitrogen atom a heterocyclic ring and wherein of R and R^1 one stands for hydrogen or for a phenyl radical which may optionally be substituted by halogen or alkoxy radicals of not more than 4 carbon atoms and the other stands for a phenyl radical which may optionally be substituted by halogen or alkoxy radicals of not more than 4 carbon atoms.

The new pteridin derivatives of this invention are active against schistosomiasis in experimental animals.

According to a further feature of the invention we provide a process for the manufacture of the said new pteridin derivatives which comprises heating together a diamino-pyridine derivative of the formula



wherein X and X^1, Y and Y^1 have the significance stated above and an α-diketone of the formula R.CO.CO.R^1 wherein R and R^1 have the significance stated above. The said diamino-pyrimidines are claimed in co-pending Application No. 20541/54 (Serial No. 763,120) and may be obtained by the process therein described and claimed.

In this process there may be used, in place of the stated α-diketones also their functional derivatives, for example their oximes or phenylhydrazones.

According to a further feature of the invention we provide a process for the manufacture of the said new pteridin derivatives which comprises oxidation of the corresponding 7:8-dihydropteridins such as those claimed in co-pending Application No. 1885/55 (Serial No. 763,138) and which themselves may be obtained by the process described and claimed in co-pending Application No. 1885/55 (Serial No. 763,138).

In this specification the numbering of the pteridin ring system is that of "The Ring Index" by Capell and Patterson (Reinhold Publishing Corporation, New York, 1940).

The invention is illustrated but not limited by the following Examples in which the parts are by weight.

EXAMPLE 1.

6.8 Parts of 2:4-bismethylamino-5:6-diaminopyrimidine, 9 parts of benzil and 180 parts of ethanol are heated together for 5 hours under reflux in an atmosphere of nitrogen. The solution is cooled and filtered when 2:4-bismethylamino-6:7-diphenylpteridin of m.p. 261° C. is obtained. Similarly, using appropriately substituted benzil derivatives, there may be obtained 2:4-bismethylamino-6:7-di-*o*-chlorophenylpteridin, m.p. 263° C., 2:4-bismethylamino-6:7-di-*m*-chlorophenylpteridin, m.p. 254° C. and 2:4-bismethylamino-6:7-di-*p*-chlorophenylpteridin, m.p. 323° C.

EXAMPLE 2.

The 2:4-bismethylamino-5:6-diaminopyrimidine in the process of Example 1 is replaced by an equivalent amount of 2-methylamino-4-dimethylamino-5:6-diamino-

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pyrimidine when there is obtained 2-methylamino- 4-dimethylamino-6:7-diphenylpteridin of m.p. 306° C.

EXAMPLE 3.

The 2:4 - bismethylamino-5:6-diaminopyrimidine in the process of Example 1 is replaced by an equivalent amount of 2-dimethylamino - 4-methylamino-5:6-diaminopyrimidine when there is obtained 2-dimethylamino - 4-methylamino-6:7-diphenylpteridin of m.p. 210° C.

EXAMPLE 4.

The 2:4 - bismethylamino-5:6-diaminopyrimidine in the process of Example 1 is replaced by an equivalent amount of 2:4-bisdimethylamino - 5:6 - diaminopyrimidine when there is obtained 2:4-bisdimethylamino-6:7-diphenylpteridin of m.p. 212° C.

By using an equivalent amount of an appropriately substituted 5:6 - diaminopyrimidine there is obtained:— 2-dimethylamino - 4-diethylamino-6:7-diphenylpteridin, m.p. 169° C., 2-dimethylamino-4-morpholino-6:7-diphenylpteridin, m.p. 216° C., 2-dimethylamino - 4 - isopropylamino - 6:7-diphenylpteridin, m.p. 218° C., 2-dimethylamino - 4 - ethylamino-6:7-diphenylpteridin, m.p. 181° C., 2-dimethylamino-4-*n*-butylamino-6:7-diphenylpteridin, m.p. 128° C., 2 - dimethylamino-4-piperidino-6:7-diphenylpteridin, m.p. 207° C., 2-dimethylamino-4-*n*-propylamino - 6:7-diphenylpteridin, m.p. 240° C., 2-diethylamino-4-methylamino-6:7-diphenylpteridin, m.p. 229° C., 2-ethylamino-4 - methylamino - 6:7-diphenylpteridin, m.p. 249° C., and 2-piperidino-4-methylamino-6:7-diphenylpteridin, m.p. 204° C.

EXAMPLE 5.

8 Parts of 2:4 - bismethylamino-5:6-diaminopyrimidine sulphate, 9.8 parts of anisil, 200 parts of ethanol, 75 parts of water and 20 parts of crystallised sodium acetate are heated together under reflux for 10 hours. The mixture is cooled and filtered, and the solid is dried and extracted with light petroleum (100—120° C.). The residue is then crystallised from a mixture of equal parts of ethanol and of dimethylformamide. 2:4 - Bis - methylamino-6:7-di-*p*-methoxyphenylpteridin, m.p. 260° C., is obtained.

EXAMPLE 6.

5 Parts of 2:4-bisdimethylamino-6:7-diphenyl-7:8-dihydropteridin are dissolved in 2000 parts of ethanol and the solution is made alkaline by addition of aqueous ammonia of specific gravity 0.880 and evaporated to one third of its volume. It is then filtered and the solid is washed with water. It is then suspended in 300 parts of 2N-sulphuric acid and treated with a slight excess of saturated potassium permanganate solution. It is then basified with aqueous ammonia and filtered. The solid is washed, dried and extracted with boiling ethyl acetate. The extract is evaporated and cooled and filtered. The solid residue consists of 2:4-bisdimethylamino-6:7-diphenylpteridin identical with the product of Example 4.

EXAMPLE 7.

29.4 Parts of 2:4-bisdimethylamino-5:6-diaminopyrimidine sulphate, 68 parts of sodium acetate, 500 parts of water, 500 parts of ethanol and 15.2 parts of phenylglyoxalhydrate are heated together under a reflux condenser for 15 minutes. The mixture is then cooled and filtered and the solid residue is crystallised from ethanol to give 2:4-bisdimethylamino-7-phenylpteridin, m.p. 190° C. Similarly, by using an equivalent quantity of 2:4-bismethylamino - 5:6-diaminopyrimidine sulphate there is obtained 2:4-bismethylamino-7-phenylpteridin, m.p. 255° C.

EXAMPLE 8.

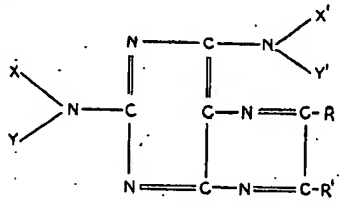
14.1 Parts of 2:4-bisdimethylamino-5:6-diaminopyrimidine sulphate, 560 parts of 6-N-sulphuric acid, 450 parts of ethanol and 7.3 parts of phenylglyoxalhydrate are heated together under reflux for 2 hours. The ethanol is then removed by distillation, the residue is cooled, purified with ammonia and filtered. The solid is crystallised from methanol and 2:4-bisdimethylamino-6-phenylpteridin, m.p. 191° C., is obtained.

EXAMPLE 9.

To 4 parts of 7-*p*-chlorophenyl-2-dimethylamino - 4 - methylamino - 6 - phenyl-7:8-dihydropteridin dissolved in 135 parts of acetone, there is added dropwise with stirring a solution of 1.1 parts of potassium permanganate in 135 parts of acetone. The mixture is filtered, and the filtrate is treated with sulphur dioxide and the solvent is removed by distillation. The solid residue is crystallised from ethanol to give 7 - *p*-chlorophenyl-2-dimethylamino-4-methylamino-6-phenylpteridin, m.p. 239° C.

What we claim is:—

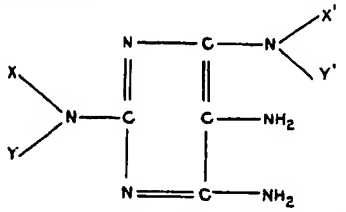
1. New pteridin derivatives of the formula:—



wherein X and X^1 stand for alkyl and Y and Y^1 stand for alkyl or hydrogen, wherein X and Y and X^1 and Y^1 may optionally be joined to form together with the adjacent nitrogen atom a heterocyclic ring and wherein of R and R^1 one stands for hydrogen or for a phenyl radical which optionally may be substituted by halogen or alkoxy radicals of not more than 4 carbon atoms and the other stands for a phenyl radical which may optionally be substituted by halogen or alkoxy radicals of not more than 4 carbon atoms.

2. Process for the manufacture of the new pteridin derivatives claimed in Claim 1 which

comprises heating together a diaminopyrimidine derivative of the formula



wherein X and X^1, Y and Y^1 have the significance stated in Claim 1 and an α-diketone of the formula R.CO.CO.R^1 wherein R and R^1 have the significance stated in Claim 1.

3. A process as claimed in Claim 2 wherein there is used, in place of the stated α-diketones their functional derivatives, for example their oximes or phenylhydrazones.

4. Process for the manufacture of the new pteridin derivatives claimed in Claim 1 which comprises oxidation of the corresponding 7:8-dihydropteridins.

5. Process for the manufacture of pteridin derivatives as hereinbefore described especially with reference to the foregoing Examples.

ALFRED O. BALL,
Agent for the Applicants.

PROVISIONAL SPECIFICATION

Pteridin Derivatives

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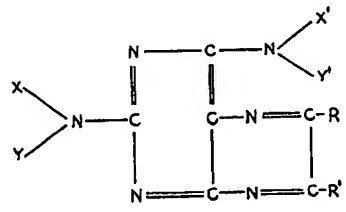
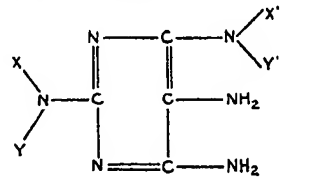


wherein X and X^1 stand for alkyl and Y and Y^1 stand for alkyl or hydrogen, wherein X and Y and X^1 and Y^1 may optionally be joined to form together with the adjacent nitrogen atom a heterocyclic ring and wherein R and R^1 stand for hydrogen, hydrocarbon radicals or substituted hydrocarbon radicals.

According to a further feature of the invention we provide a process for the manufacture of the said new pteridin derivatives which comprises heating together a diaminopyrimidine derivative of the formula



wherein X and X^1, Y and Y^1 have the significance stated above and an α-diketone of the formula R.CO.CO.R^1 wherein R and R^1 have the significance stated above.

In this process there may be used, in place of the stated α-diketones also their functional derivatives, for example their oximes or phenylhydrazones.

According to a further feature of the invention we provide a process for the manufacture of the said new pteridin derivatives which comprises oxidation of the corresponding dihydropteridins.

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EXAMPLE 2.

The 2:4-bismethylamino-5:6-diaminopyrimidine in the process of Example 1 is replaced by an equivalent amount of 2-methylamino-4-dimethylamino-5:6-diaminopyrimidine when there is obtained 2-methylamino 4-methylamino-6:7-diphenylpteridin of m.p. 306° C.

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The 2:4-bismethylamino-5:6-diaminopyrimidine in the process of Example 1 is replaced by an equivalent amount of 2-dimethylamino-4-methylamino-5:6-diaminopyrimidine when there is obtained 2-dimethylamino-4-methylamino-6:7-diphenylpteridin of m.p. 210° C.

EXAMPLE 4.

The 2:4-bismethylamino-5:6-diaminopyrimidine in the process of Example 1 is replaced by an equivalent amount of 2:4-bismethylamino-5:6-diaminopyrimidine when there is obtained 2:4-bisdimethylamino-6:7-diphenylpteridin of m.p. 212° C.

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